Influenza vaccine to reduce adverse vascular events in patients with heart failure: a multinational randomised, double-blind, placebo-controlled trial

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Summary

Background Influenza increases the risk of cardiovascular events and deaths. We aimed to see whether influenza vaccination reduces death and vascular events in patients with heart failure.

Methods We did a pragmatic, randomised, double-blind, placebo-controlled trial in 30 centres (mostly hospitals affliated with universities or a research institute) in ten countries in Asia, the Middle East, and Africa (7 in India, 4 in Philippines, 4 in Nigeria, 6 in China, 1 in Zambia, 2 in Mozambique, 3 in Saudi Arabia, 1 in Kenya, 1 in Uganda, and 1 in United Arab Emirates). Participants (aged ≥18 years; 52·1% female; not disaggregated by race or ethnicity) with heart failure (New York Heart Association class II, III, or IV) were randomly assigned (1:1) by a centralised web-based system with block randomisation stratified by site, to receive 0·5 ml intramuscularly once a year for up to 3 years of either inactivated standard dose influenza vaccine or placebo (saline). We excluded people who had received influenza vaccine in 2 of the previous 3 years, and those likely to require valve repair or replacement. Those who administered assigned treatments were not masked and had no further role in the study. Investigators, study coordinators, outcome adjudicators, and participants were masked to group assignment. The first of two co-primary outcomes was a first-event composite for cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke, and the second was a recurrent-events composite for cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, and hospitalisation for heart failure. Outcomes were assessed every 6 months in the intention-to-treat population. Secondary outcomes were all-cause death, cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, all-cause hospitalisation, hospitalisation for heart failure, and pneumonia, both overall and during periods of peak influenza exposure. This study is registered with ClinicalTrials.gov, NCT02762851.

Findings Between June 2, 2015, and Nov 21, 2021, we enrolled 5129 participants and randomly assigned (1:1) 2560 (50·0%) to influenza vaccine and 2569 (50·0%) to placebo. The first co-primary outcome occurred in 380 (14·8%) of 2560 participants in the vaccine group and 410 (16·0%) of 2569 participants in the placebo group (hazard ratio [HR] 0·93 [95% CI 0·81–1·07]; p=0·30). The second co-primary outcome occurred in 754 (29·5%) of 2560 participants in the vaccine group and 819 (31·9%) of 2569 participants in the placebo group; HR 0·92 [95% CI 0·84–1·02]; p=0·12). The secondary outcomes of all-cause hospitalisations (HR 0·84 [95% CI 0·74–0·97]; p=0·013) and pneumonia (HR 0·58 [0·42–0·80]; p=0·0006) were significantly reduced in the vaccine group compared with in the placebo group but there was no significant difference between groups for all-cause death, cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, and hospitalisation for heart failure. In a prespecified analysis, in which events were limited to periods of peak influenza circulation, the first co-primary outcome, and the secondary outcomes of all-cause death, cardiovasular death, and pneumonia were significantly lower in the vaccinated group than in the placebo group, whereas the second co-primary outcome and the secondary outcomes of non-fatal myocardial infarction, non-fatal stroke, all-cause hospitalisation, and hospitalisation for heart failure were not significantly lower.

Interpretation Although the prespecified co-primary outcomes during the entire period of observation were not statistically significant, the reduction during the peak influenza circulating period suggests that there is likely to be a clinical benefit of giving influenza vaccine, given the clear reduction in pneumonia, a moderate reduction in hospitalisations, and a reduction in cardiovascular events and deaths during periods of peak circulation of influenza. Taken in conjunction with previous trials and the observational studies, the collective data suggest benefit.

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Research in context

Evidence before this study

We searched PubMed on March 3, 2022, for research articles published from database inception to March 4, 2022, with no language restrictions, using the search terms "influenza" AND "vaccine" AND "cardiac". We retrieved five randomised trials, none of which were limited to participants with heart failure. One trial of 5260 patients with a recent cardiac hospitalisation reported no significant difference in outcomes between high-dose and standard-dose influenza vaccine. A trial in 2571 participants with acute coronary disease reported that standard-dose influenza vaccine reduced cardiovascular events at 12 months compared with placebo. A trial of 439 participants with acute coronary syndrome reported that influenza vaccine reduced a composite cardiac outcome compared with no vaccine. A trial of 658 participants with stable coronary disease reported that influenza vaccine reduced a composite cardiac outcome compared with placebo. One trial in 301 participants with acute ischaemic heart disease reported a reduction in cardiovascular death in the vaccine group compared with the no treatment group.

Added value of this study

To our knowledge, this is the first placebo-controlled trial of influenza vaccine in patients with heart failure. Although the influenza vaccine did not significantly reduce the first or second primary composite outcome, the vaccine reduced all-cause hospitalisation by 16% and reduced community-acquired pneumonia by 42%. When, in a prespecified secondary analysis, we analysed events during peak circulation of influenza, the first primary outcome (a composite of first event for death, non-fatal myocardial infarction, or non-fatal stroke) was significantly reduced in participants randomly assigned to receive influenza vaccine. A similar pattern of fewer events was seen in peak periods of influenza circulation, and in seasons during which the strain in the vaccine was similar to the predominant circulating strain.

Implications of all the available evidence

Taken in conjunction with previous trials and previous observational studies, the collective data suggest benefit and the importance of vaccinating patients with heart failure against influenza.

Introduction

Heart failure poses a major global burden to health. It has been estimated that the number of patients with heart failure has nearly doubled from 33·5 million in 1990 to 64·3 million in 2017.[1] All-cause first-year rates of death due to heart failure have been estimated to be 23·0 per 100 person-years.[2]

Influenza infection has been associated with increased risk of cardiovascular events and death.[3–7] A lower rate of cardiovascular events related to ischaemia has been reported for influenza vaccination in observational studies,[8–11] pooled data from randomised trials,[12] and a placebo-controlled trial.[13] A systematic review[14] that pooled data from six cohort studies reported a 17% reduction in all-cause mortality with influenza vaccination in patients with heart failure. A randomised trial[15] of high-dose versus standard-dose inactivated influenza vaccine, which included patients with ischaemic heart disease and heart failure, did not show a difference in cardiovascular outcomes during influenza seasons between the two study groups.

Given the increasing burden of heart failure in low-income and middle-income countries,[16] and that use of routine influenza vaccination in them is extremely low, we did a randomised controlled trial in these locations.

See Online for appendix

Methods

Study design and participants

This pragmatic, double-blind, placebo-controlled, randomised trial compared inactivated influenza vaccine versus placebo for the prevention of cardiovascular outcomes in patients with heart failure. The study was done at 30 sites (mostly hospitals affiliated with universities or a research institute) in ten countries in Asia (China, India, and Philippines), the Middle East (Saudi Arabia and United Arab Emirates), and Africa (Kenya, Mozambique, Nigeria, Uganda, and Zambia) over three influenza seasons.[17] Most participants were recruited either from heart failure clinics located within study institutions or through local investigators' databases of patients with heart failure.

Patients aged 18 years or older with a clinical diagnosis of heart failure and New York Heart Association (NYHA) functional classification of heart failure II, III, or IV were eligible. Exclusion criteria included a contraindication to influenza vaccine, receipt of influenza vaccine in two of the previous three years, and severe valvular disease if surgical or percutaneous valve repair or replacement was likely. Detailed eligibility criteria are summarised in the appendix (p 5).

Ethics approval was obtained from the research ethics boards of all participating centres before the start of the study. Although most sites obtained ethics approval individually, in Philippines and Mozambique, the national lead investigator obtained ethics approval on behalf of all sites within the country. Regulatory approvals were obtained according to the requirements of each country, in which the time for obtaining regulatory approvals ranged from 6 to 18 months. All participants provided written informed consent, which was obtained annually.

The use of a placebo in this trial is in keeping with WHO expert consultation on the use of placebos in

vaccine trials,[18] as the study was done at sites where influenza vaccine was not provided to most patients and barriers to access were unlikely to be overcome throughout the duration of the trial. Use of an active comparator such as a high-dose vaccine was not possible because the vaccine was not licenced at low-income and middle-income trial sites. In doing this placebo-controlled trial, we excluded individuals who had previously had an influenza vaccination in two of the three previous seasons, and we allowed participants to receive influenza vaccine outside of the trial if their physicians considered it necessary. The study was done in a population with a high cardiovascular burden and was therefore of high potential public health value and responsive to local health needs.[18] This study began as a pilot study on June 2, 2015 (NCT01945268) and then continued as a full trial on May 5, 2016. This study is registered with ClinicalTrials.gov, NCT02762851 and is closed to new participants.

Randomisation and masking

Participants were randomly assigned (1:1) to inactivated influenza vaccine or placebo, by use of a list generated before the start of the study by a centralised web-based system with block randomisation stratified by site.

Investigators, study coordinators, outcome adjudicators, and participants were masked to group assignment. Study drugs were administered by vaccine administrators who were aware of group assignments but had no other role in the trial. If a participant was assigned to placebo, the vaccine administrator would prepare a saline syringe in a separate room from the participant to avoid unmasking them (once filled, influenza vaccine and placebo syringes were indistinguishable). The vaccine or placebo syringe was administered in a separate room from where the assignment of the study intervention occurred, to maintain masking of the participants and study team.

Procedures

Participants received a 0·5 ml dose of inactivated influenza vaccine recommended for the influenza season or placebo (saline) once a year intramuscularly for up to three consecutive influenza seasons. We used a trivalent influenza vaccine formulation, unless a quadrivalent one was available and licensed in that study country. The study protocol was amended in February, 2019, to allow for quadrivalent vaccine if it became licensed in a study country. The trivalent vaccine contained 15 µg of haemagglutinin per 0·5 ml dose for each of the two influenza type A subtypes (H1N1 and H3N2) and for one of the two influenza type B lineages (Yamagata and Victoria), or both type B lineages for the quadrivalent vaccine, for the southern or northern hemispheres, as recommended by WHO (appendix p 6).

The co-primary outcomes were assessed at study centres by trial staff by direct communication with the participant (or next of kin), by either a clinic visit or a telephone call plus review of medical records. Outcomes were assessed every 6 months. The shipping of the study vaccine or placebo to study sites was coordinated with the manufacturer of the vaccine. In China and India, the study vaccine was sent from the vaccine manufacturing plant within that country, whereas for all other counties, the study vaccine was sent from Canada following receipt from the manufacturer in France. The vaccine came in prefilled syringes and was kept in a dark container at 2–8°C. Upon vaccine receipt, study sites downloaded temperature data from the temperature monitoring device and completed an acknowledgment document to confirm that the vaccine had been received in the proper condition. Any temperature deviation was reported immediately to the manufacturer, which would determine whether the vaccine was viable and if it was not, a second shipment was sent to the site using backup doses stored in Canada. Influenza vaccines were stored in certified pharmaceutical refrigerators with a backup source of power, and temperatures were monitored every 24 h, with records forwarded to the coordinating centre weekly.

	All (n=5129)	Influenza vaccine (n=2560)	Placebo (n=2569)
Mean age, years	57·2 (15·3)	57·4 (15·1)	57·0 (15·6)
Mean heart rate, beats per min	80·3 (15·0)	80·3 (15·1)	80·3 (14·9)
Mean systolic blood pressure, mm Hg	125·7 (23·7)	125·8 (23·3)	125·6 (24·1)
Sex			
Female	2638 (51·4%)	1333 (52·1%)	1305 (50·8%)
Male	2491 (48·6%)	1227 (47·9%)	1264 (49·2%)
Region			
China	694 (13·5%)	348 (13·6%)	346 (13·5%)
India	1171 (22·8%)	583 (22·8%)	588 (22·9%)
Africa	2051 (40·0%)	1023 (39·9%)	1028 (40·0%)
Philippines	718 (14·0%)	359 (14·0%)	359 (14·0%)
Middle East	495 (9·7%)	247 (9·6%)	248 (9·7%)
NYHA class of heart failure			
Class II	3563 (69·5%)	1773 (69·3%)	1790 (69·7%)
Class III	1340 (26·1%)	683 (26·7%)	657 (25·6%)
Class IV	226 (4·4%)	104 (4·1%)	122 (4·7%)
Left ventricular function*			
Preserved (>50%)	1157 (22·6%)	560 (21·9%)	597 (23·2%)
Mild (LVEF 40–49%)	863 (16·8%)	441 (17·2%)	422 (16·4%)
Moderate (LVEF 31–39%)	1250 (24·4%)	621 (24·3%)	629 (24·5%)
Severe (LVEF ≤30%)	1621 (31·6%)	821 (32·1%)	800 (31·1%)
Unknown or missing	238 (4·6%)	117 (4·6%)	121 (4·7%)
Heart failure first diagnosis			
Study enrolment	296 (5·8%)	143 (5·6%)	153 (6·0%)
<1 year ago	1447 (28·2%)	692 (27·0%)	755 (29·4%)
1–5 years ago	2210 (43·1%)	1139 (44·5%)	1071 (41·7%)
>5 years ago	1149 (22·4%)	574 (22·4%)	575 (22·4%)
Unknown or missing	27 (0·5%)	12 (0·5%)	15 (0·6%)

(Table 1 continues on next page)

	All (n=5129)	Influenza vaccine (n=2560)	Placebo (n=2569)
(Continued from previous page)			
Previous stroke	409 (8·0%)	202 (7·9%)	207 (8·1%)
Previous myocardial infarction	1060 (20·7%)	546 (21·3%)	514 (20·0%)
Chronic obstructive pulmonary disease	257 (5·0%)	136 (5·3%)	121 (4·7%)
Hypertension	3329 (64·9%)	1661 (64·9%)	1668 (64·9%)
Chronic kidney disease	343 (6·7%)	176 (6·9%)	167 (6·5%)
Hospitalisation for heart failure in the previous year	1553 (30·3%)	773 (30·2%)	760 (29·6%)
Type 2 diabetes	1160 (22·6%)	570 (22·3%)	590 (23·0%)
Hyperlipidaemia	846 (16·5%)	419 (16·4%)	427 (16·6%)
Heart rhythm			
Sinus	4509 (87·9%)	2268 (88·6%)	2241 (87·2%)
Atrial fibrillation	530 (10·3%)	248 (9·7%)	282 (11·0%)
Cause of heart failure			
Ischaemic	1528 (29·8%)	773 (30·2%)	755 (29·4%)
Hypertensive	1968 (38·4%)	983 (38·4%)	985 (38·3%)
Idiopathic	752 (14·7%)	379 (14·8%)	373 (14·5%)
Valvular	283 (5·5%)	130 (5·1%)	153 (6·0%)
Other	598 (11·7%)	295 (11·5%)	303 (11·8%)
Medications			
β blocker	3095 (60·3%)	1545 (60·4%)	1550 (60·3%)
ACE inhibitor or angiotensin receptor blocker	3688 (71·9%)	1853 (72·4%)	1835 (71·4%)
Aldosterone inhibitor	2439 (47·6%)	1232 (48·1%)	1207 (47·0%)
Other diuretics	3383 (66·0%)	1702 (66·5%)	1681 (65·4%)
Long-acting nitrate	758 (14·8%)	370 (14·5%)	388 (15·1%)
Digoxin	1185 (23·1%)	597 (23·3%)	588 (22·9%)
Aspirin or thienopyridines	3077 (60·0%)	1543 (60·3%)	1534 (59·7%)
Vitamin K antagonists	505 (9·8%)	263 (10·3%)	242 (9·4%)
Direct oral anticoagulants	73 (1·4%)	35 (1·4%)	38 (1·5%)

Data are mean (SD) or n/N (%). ACE=angiotensin-converting enzyme. LVEF=left ventricular ejection fraction. NYHA=New York Heart Association functional classification. *Determined by the study site.

Table 1: **Baseline characteristics**

For more on the **WHO Global Influenza Surveillance and Response System** see https://www.who.int/initiatives/global-influenza-surveillance-and-response-system

For the **WHO Global Influenza Programme influenza surveillance outputs** see https://www.who.int/teams/global-influenza-programme/surveillance-and-monitoring/influenza-surveillance-outputs

We used data from WHO,[19] and public health reports or published studies from each study country, to determine the optimal timing for influenza vaccination (ie, November–December *vs* April–May). In Kenya, Mozambique, Nigeria, and Zambia, influenza circulates throughout the year, although peak periods of circulation still occur. In these countries, participants were enrolled in either October–November (autumn cohort) or April–May (spring cohort), which was an amendment to our original protocol to allow us to increase enrolment.[17] After randomisation, participants were contacted at 6-month intervals. All study sites used an electronic data capture system.

We assessed participants for any severe immediate reactions (eg, severe hypersensitivity reactions) and adverse events by having the vaccination nurse monitor participants after the injection. In keeping with WHO guidance on the clinical evaluation of vaccines, details of serious adverse events were collected from all randomly assigned participants throughout the trial.[20] Unsolicited adverse events and serious adverse events were recorded at follow-up visits.

Outcomes

Our original protocol specified a single primary composite outcome (cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, and hospitalisations for heart failure, each defined using standard criteria; appendix pp 2–3). Before trial completion, on Oct 19, 2021, we changed this outcome to two co-primary outcomes, given uncertainty in cohort studies[14] about the effectiveness of influenza vaccination. We excluded hospitalisations from the first co-primary outcome and added recurrent events and hospitalisation in the second co-primary outcome. The first co-primary outcome was time to first-event composite of cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke. The second co-primary outcome was a recurrent-events composite of cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, or hospitalisation for heart failure. Deaths from unknown causes were categorised as cardiovascular deaths.[20] We included non-fatal myocardial infarction and non-fatal stroke as part of the primary outcome on the basis of observational studies of influenza-related risk,[21] with the potential causal mechanism being the occurrence of plaque rupture or endothelial-cell dysfunction in heart failure patients.[22] A prespecified subanalysis examined events that occurred during peak periods of influenza circulation, as identified via WHO Global Influenza Surveillance and Response System data and WHO Global Influenza Programme Influenza Surveillance Reports (appendix p 8). If WHO data for a country were not available, we used regional reports if available, or data from a geographically contiguous country.

Secondary outcomes were deaths, hospitalisations, and pneumonia, both overall and during periods of peak influenza circulation.

Statistical analysis

We estimated that 5000 participants would be needed to be followed up for 3 years for the study to have more than 80% power to detect a reduction in events in the primary composite outcome from 17% in the control group to 14% in the vaccine group.[17] We changed the sample size by a protocol amendment. We assumed that 250 events per group, or 10% of adverse vascular events, would be independent of influenza. This would leave 2250 events in each group. A 25% attack rate of influenza in the control group equated to 562 cases, and a similarly defined 15% attack rate in the vaccine group (assuming an influenza risk reduction of 40% with the vaccine) equated to 338 influenza cases in vaccine group. We then assumed that 30% of these influenza infections would result in adverse vascular events in 168 patients in the vaccine group, and 101 patients in the

placebo group. Adding back in the 250 adverse vascular events that were independent of influenza vaccination to each group led to 418 (17% of 2500 participants) adverse vascular events in the control group and 351 (14% of 2500 participants) adverse vascular events in the vaccine group, for 83% power to detect this difference between groups.

For the primary analysis, events during and outside of peak influenza circulation periods were analysed together for the first and second co-primary composite outcomes. Analysis was by intention to treat (ie, by the group to which participants were assigned), with the follow-up period calculated as the time from randomisation to the last reported contact time. Events during the first 2 weeks after assigned treatment were excluded from the analysis. Only investigator-observed values were used in the analysis. If an event date was not known, we used the middle date of the period (eg, week) in which the event was known to have occurred. We used a step-down fallback approach to test for the first primary composite outcome with a two-sided α of 0·04.[23] If the first co-primary composite outcome, a time to first event analysis using the standard log-rank test, was not significant with an α of 0·04, then we would test the second primary composite, which was for recurrent events, using the Andersen-Gill model[24] and a two-sided α of 0·01. All tests of significance were two-sided. Hazard ratios (HRs) and corresponding two-sided 95% CIs were estimated using the Cox proportional hazards model, with no covariates other than study vaccine were included in the model. Kaplan–Meier estimates of cumulative risk and cumulative hazard functions were constructed. We did prespecified secondary analyses of events occurring within and outside of peak influenza circulation periods, for time to first event, both for the first and second co-primary outcomes. We also did analyses of recurrent hospitalisations for heart failure and all-cause hospitalisations. Since secondary outcome analyses are considered exploratory, no adjustment was made for the multiple comparisons. The plausibility of the proportional hazards assumption was assessed by visually examining both the plot of the log of the negative log of Kaplan–Meier estimates of the survival function versus the log of time for evidence of non-parallelism and by testing the significance of a time–treatment interaction term in the Cox model (time log transformed).

As part of the prespecified secondary analysis, we derived estimates of peak periods of influenza circulation and did analysis of events that occurred during these periods (appendix pp 8–11).[25] We also did similar analyses of events that occurred outside of peak periods of influenza circulation.

We used available data to help determine the predominant influenza strain that was circulating, and whether this strain was similar to that in the vaccine strain (appendix pp 8–11). As specified in our protocol, we assessed the effects of the vaccine in such seasons and in seasons in which the strains did not appear to be similar.

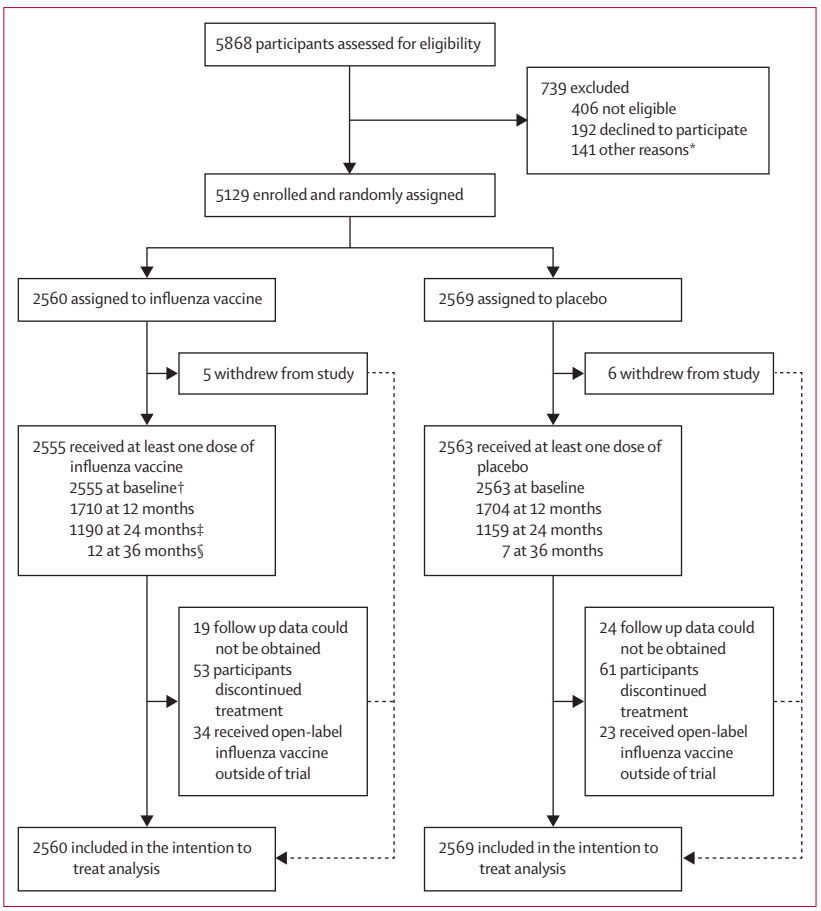

Figure: **Trial profile**
*Details were reported in study logs that are no longer accessible to the authors. †All participants who received the assigned treatment at 12 months, 24 months, or 36 months received it at baseline. ‡30 (2·5%) of 1190 participants in the vaccine group and 30 (2·5%) of 1190 participants in the placebo group received assigned treatment at 24 months but not at 12 months. §One (8·3%) of 12 participants who received placebo at 36 months did not receive it at 12 months. All other participants had received the assigned treatment the previous year.

A prespecified subgroup analysis compared the effect of influenza vaccination on outcomes among participants with severe heart failure (NYHA class III–IV) and in those with less severe heart failure (NYHA class I–II). Although an analysis by subtype of heart failure was not planned, we did a post-hoc subgroup analysis by cause of ischaemic heart failure.

All statistical analyses for the trial were done by use of SAS software (version 9.4). The study began as a pilot study on June 2, 2015 (NCT01945268) and continued as a full trial on May 5, 2016 (NCT02762851) and is closed to new participants.

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Between June 2, 2015, and Nov 21, 2021, 5129 participants (mean age 57·2 [SD 15·3] years; 51·4% female; data not disaggregated by race or ethnicity) were enrolled and randomly assigned to influenza vaccine (n=2560) or placebo (n=2569; table 1, figure). The mean duration of follow-up was 2·3 (SD 0·9) years. 4903 (95·6%) of 5129 participants had NYHA class II or III heart failure. The most common causes of heart failure were ischaemia (1528 [29·8%]) and hypertension (1968 [38·4%]). 3916 (76·4%) of 5129 participants were enrolled at sites in India, Africa, and China. 1060 (20·7%) of 5129 participants had previously had an myocardial infarction and 1160 (22·6%) had type 2 diabetes. Participant characteristics were similar between the two groups (table 1). None of the participants received the influenza vaccine in the year before enrolling in the trial.

Follow-up ended early in seven (70%) of the ten countries. Owing to COVID-19 restrictions, follow-up ended early in Philippines, Nigeria, Mozambique, and Saudi Arabia. Before the pandemic, follow-up ended early in China (on April 20, 2019 because vaccine could not be obtained locally), Kenya (on Dec 20, 2018 because regulatory approval for new vaccine shipments could not be obtained), and Uganda (on Jan 21, 2019 because the site investigator relocated). 5118 (99·8%) of 5129 participants received at least one dose of study vaccine or placebo. 11 participants withdrew after randomisation but before receiving the study vaccine (figure). All participants who received the assigned treatment at 12 months, 24 months, or 36 months received the initial assigned treatment at baseline. 60 participants (30 in each group) received the assigned treatment at 24 months but not at 12 months. One participant received placebo at 36 months but not at 12 months. All other participants had received the assigned treatment the previous year. No follow-up data could be obtained for 19 participants in the influenza vaccine group and 24 participants in the placebo group. Over the course of the trial, 114 participants discontinued treatment (53 in the influenza vaccine group and 61 in the placebo group). 57 participants received open-label influenza vaccine outside of the trial (34 [1·3%] in the influenza group and 23 [0·9%] in the placebo group). The only participants to receive the quadrivalent vaccine were those enrolled in India, and only during the 2019 northern hemisphere and 2020 southern hemisphere influenza seasons. These recipients represented a small proportion of participants (122 [10·8%] of all vaccines given at that timepoint, or 2·3% of all vaccines given during the entire study).

There was no significant difference between the influenza vaccine and placebo groups in the first co-primary outcome (380 [14·8%] participants *vs* 410 [16·0%] participants; HR 0·93 [95% CI 0·81–1·07]; p=0·30) or the second co-primary outcome (754 [29·5%] recurrent events *vs* 819 [31·9%] recurrent events; HR 0·92 [0·84–1·02]; p=0·12; table 2, appendix p 14). 427 (16·7%) participants died in the vaccine group versus 473 (18·4%) participants in the placebo group (HR 0·90 [95% CI 0·79– 1·03]; p=0·13).

Fewer individuals had all-cause hospitalisation in the vaccine group than in the placebo group (388 participants [15·2%] *vs* 455 participants [17·7%]; HR 0·84 [95% CI 0·74–0·97]; p=0·013) and there were fewer recurrent all-cause hospitalisations in the vaccine group than in the placebo group (557 participants [21·8%] *vs* 671 participants [26·1 %]; HR 0·84 [95% CI 0·75–0·94]; p=0·0022). There were fewer participants with pneumonia in the vaccine group than in the placebo group (61 [2·4%] participants *vs* 104 [4·0 %] participants; HR 0·58 [95% CI 0·42–0·80]; p=0·0006). These differences were observed over the entire period of observation. None of the other secondary outcomes were significantly reduced in the vaccine group compared with the placebo group.

In the prespecified analyses, which was restricted to events during peak circulating influenza periods, there were lower rates of the first co-primary outcome in the

	Number of events		Hazard ratio (95% CI)	p value
	Influenza vaccine group (n=2560)	Placebo group (n=2569)		
First events				
First co-primary outcome of cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke	380 (14·8%)	410 (16·0%)	0·93 (0·81–1·07)	0·30
Second co-primary outcome of cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke, hospitalisation for heart failure	524 (20·5%)	570 (22·2%)	0·92 (0·81–1·03)	0·15
Secondary outcomes				
Death—all cause	427 (16·7%)	473 (18·4%)	0·90 (0·79–1·03)	0·13
Death—cardiovascular	334 (13·0%)	374 (14·6%)	0·89 (0·77–1·04)	0·13
Death—non-cardiovascular	93 (3·6%)	99 (3·9%)	0·94 (0·71–1·25)	0·68
Non-fatal myocardial infarction	21 (0·8%)	23 (0·9%)	0·91 (0·50–1·65)	0·76
Non-fatal stroke	47 (1·8%)	43 (1·7%)	1·10 (0·73–1·66)	0·66
Hospitalisation—all causes	388 (15·2%)	455 (17·7%)	0·84 (0·74–0·97)	0·013
Hospitalisation—for heart failure	245 (9·6%)	277 (10·8%)	0·88 (0·74–1·05)	0·15
Pneumonia	61 (2·4%)	104 (4·0%)	0·58 (0·42–0·80)	0·0006
Recurrent events				
Second co-primary outcome of cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, or hospitalisation for heart failure	754 (29·5%)	819 (31·9%)	0·92 (0·84–1·02)	0·12
Secondary outcomes				
Hospitalisation—all causes	557 (21·8%)	671 (26·1%)	0·84 (0·75–0·94)	0·0022
Hospitalisation—for heart failure	346 (13·5%)	377 (14·7%)	0·92 (0·80–1·07)	0·28

Data are n (%) or hazard ratio (95% CI). Excludes events during the 2-week period following vaccination and events occurring after administrative censoring; for the first co-primary outcomes, 20 events in the influenza group and 10 in the placebo group were excluded; for recurrent events, 82 events in the influenza group and 79 in the placebo group were excluded. Three events occurred after administrative censoring: one death in the influenza group, one death in the placebo group, and one case of pneumonia in the placebo group.

Table 2: **Events by treatment group**

vaccine group than in the placebo group (193 [7·5%] participants in vaccine group *vs* 237 [9·3%] participants in the placebo group; HR 0·82 [95% CI 0·68–0·99]; p=0·038). There was no significant difference between the two groups for the second co-primary outcome (270 [10·5%] *vs* 307 [12·0%]; 0·88 [0·74–1·03]; p=0·11; table 3; appendix p 15). In the vaccine group compared with the placebo group, there were fewer all-cause deaths (212 [8·3%] participants in the vaccine group *vs* 269 [10·5%] participants in the placebo group; HR 0·79 [95% CI 0·66–0·95]; p=0·0099), cardiovascular deaths (170 [6·6%] *vs* 221 [8·6%]; HR 0·77 [0·63–0·94]; p=0·0099), and episodes of pneumonia (28 [1·1%] *vs* 54 [2·1%]; HR 0·51 [0·32–0·81]; p=0·0034).

When events outside of peak influenza season were analysed, there was no difference between the influenza vaccine and placebo groups for the first or second primary outcomes, all cause death, or cardiovascular death or for all-cause hospitalisation and pneumonia (table 3). There were fewer participants with pneumonia in the influenza vaccine group than in the placebo group (33 [1·3%] participants *vs* 50 [2·0%] participants; HR 0·65 [95% CI 0·42–1·01]; p=0·054; table 3). It should be noted that differences between groups in the peak influenza period were larger than the differences in the non-peak period, but given that the patients at risk were the same individuals, no formal statistical tests of interaction were done. Unexpectedly, hospitalisation for heart failure was lower in the influenza vaccine group outside of peak influenza season (117 [4·6%] participants *vs* 153 [6·0%] participants; HR 0·76 [95% CI 0·60–0·97]; p=0·027), but not during the peak season (table 3).

For peak influenza circulation periods for seasons in which the predominant circulating influenza strain appeared to be similar to that in the influenza vaccine, there were fewer all-cause deaths (145 [5·9%] *vs* 186 [7·5%]; HR 0·78 [95% CI 0·63–0·97]), fewer cardiovascular deaths (118 [4·8%] *vs* 153 [6·2%]; 0·77 [0·61–0·98]), and fewer participants with pneumonia (16 [0·7%] *vs* 29 [1·2%]; 0·55 [0·30–1·01]) in the influenza vaccine group than in the placebo group. When the predominant circulating influenza strain was not similar to the strain in the influenza vaccine, all-cause death (67 [5·2%] *vs* 83 [6·4%]; HR 0·81 [95% CI 0·59–1·12]) and cardiovascular death (52 [4·0%] *vs* 68 [5·3%]; 0·77 [0·53–1·10]) were not significantly reduced in the influenza vaccine group compared with the placebo group. However, fewer participants had pneumonia in the influenza vaccine group than in the placebo group (12 [0·9%] *vs* 25 [2·0%]; HR 0·47 [95% CI 0·24–0·94]).

Although event rates differed by influenza season as shown in the appendix (p 12), event rates did not appear to be correlated with strain virulence, as determined by comparing placebo group event rates during seasons in which H3N2 (considered to be a more virulent strain more virulent than other influenza strains) was prevalent versus seasons when H3N2 was not prevalent. That is, pooled event rates for the placebo group were 4·6% for the primary outcome, 5·7% for all-cause death, and 5·1% for all-cause hospitalisation. By contrast, for non-H3 strains in the placebo group, the event rate was 7·9% for the primary outcome, 8·7% for all-cause death, and 7·6% for all-cause hospitalisation. Event rates by country are shown in the appendix (p 12); the number in each cell was small, and the study was not powered to formerly assess differences by region.

We found similar effects in participants who had NYHA class II versus class III–IV, and by ischaemic versus non-ischaemic causes (appendix p 13).

	Number of events during peak influenza circulation period (%)				Number of events outside of peak influenza circulation period (%)			
	Influenza vaccine (n=2560)	Placebo (n=2569)	Hazard ratio (95% CI)	p value	Influenza vaccine (n=2560)	Placebo (n=2569)	Hazard ratio	p value
Primary outcomes								
First co-primary outcome: cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke	193 (7·5%)	237 (9·3%)	0·82 (0·68–0·99)	0·038	187 (7·3%)	173 (6·8%)	1·08 (0·88–1·33)	0·45
Second co-primary outcome: cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, or hospitalisation for heart failure	270 (10·5%)	307 (12·0%)	0·88 (0·74–1·03)	0·11	254 (9·9%)	263 (10·3%)	0·96 (0·81–1·14)	0·66
Secondary outcomes								
Death—all causes	212 (8·3%)	269 (10·5%)	0·79 (0·66–0·95)	0·0099	215 (8·4%)	204 (8·0%)	1·05 (0·87–1·28)	0·59
Death—cardiovascular	170 (6·6%)	221 (8·6%)	0·77 (0·63–0·94)	0·0099	164 (6·4%)	153 (6·0%)	1·07 (0·86–1·34)	0·54
Non-fatal myocardial infarction	9 (0·4%)	13 (0·5%)	0·69 (0·29–1·61)	0·39	12 (0·5%)	10 (0·4%)	1·20 (0·52–2·77)	0·67
Non-fatal stroke	23 (0·9%)	24 (0·9%)	0·98 (0·55–1·74)	0·95	24 (1·0%)	19 (0·8%)	1·26 (0·69–2·31)	0·44
Hospitalisation—all causes	195 (7·6%)	230 (9·0%)	0·84 (0·69–1·01)	0·067	193 (7·5%)	225 (8·8%)	0·85 (0·70–1·03)	0·091
Hospitalisation—for heart failure	128 (5·0%)	124 (4·8%)	1·03 (0·80–1·31)	0·84	117 (4·6%)	153 (6·0%)	0·76 (0·60–0·97)	0·027
Pneumonia	28 (1·1%)	54 (2·1%)	0·51 (0·32–0·81)	0·0034	33 (1·3%)	50 (2·0%)	0·65 (0·42–1·01)	0·054

Data are n (%) or hazard ratio (95% CI). Data exclude events during 2-week period following vaccination and events occurring after administrative censoring.

Table 3: **Events by treatment group during and outside of peak influenza circulation periods**

	Influenza vaccine (n=2560)	Placebo (n=2569)
Serious adverse events		
Accidents and injuries		
Trauma	11 (0·4%)	11 (0·4%)
Bone fracture	4 (0·2%)	1 (<0·1%)
Falls	0	0
Anaemia	1 (<0·1%)	3 (0·1%)
Arthritis	0	1 (<0·1%)
Cardiac disorders		
Heart transplantation	1 (<0·1%)	0
Cardiac arrest	17 (0·7%)	18 (0·7%)
Unstable angina	0	0
Dementia	0	0
Venous thromboembolism, pulmonary embolus, or peripheral embolism	45 (1·8%)	53 (2·1%)
Endocrine disorders	6 (0·2%)	1 (<0·1%)
Gastrointestinal disorders	4 (0·2%)	5 (0·2%)
Haemorrhage	7 (0·3%)	14 (0·5%)
Hepatic disorders	1 (<0·1%)	3 (0·1%)
Infections and infestations	129 (5·0%)	154 (6·0%)
Laboratory-confirmed COVID-19 infection—requiring hospitalisation	2 (<0·1%)	1 (<0·1%)
Neoplasia	13 (0·5%)	12 (0·5%)
Nervous system disorders	0	0
Psychiatric disorders	0	1 (<0·1%)
Renal and urinary disorders		
Renal failure	48 (1·9%)	55 (2·1%)
Other	0	0
Respiratory disorders		
Lung disease (including COPD, asthma)	4 (0·2%)	4 (0·2%)
Respiratory failure (excluding pneumonia)	43 (1·7%)	57 (2·2%)
Surgical and medical procedures	0	1 (<0·1%)
Vascular disorders	0	0
Other	14 (0·5%)	25 (1·0%)
Other adverse events		
Felt sick after receiving study vaccination	16 (0·6%)	12 (0·5%)
Had pain, redness, or swelling in the arm at injection site	21 (0·8%)	12 (0·5%)
Pain	19 (0·7%)	11 (0·4%)
Redness	0	1 (<0·1%)
Swelling	2 (<0·1%)	0
Limitation of movement	1 (<0·1%)	0
Had other symptoms (cough)	2 (<0·1%)	3 (0·1%)
Headache	0	2 (<0·1%)
Loss of appetite	0	0
Muscle aches	0	0
Chills	0	0
Nausea	0	0
Vomiting	0	0
Diarrhoea	0	0
Rash	0	0
Fever	0	0
Eye redness	0	0
Other	1 (<0·1%)	1 (<0·1%)
Antibiotic prescription for respiratory illness excluding pneumonia	193 (7·5%)	242 (9·4%)
Laboratory-confirmed COVID-19 infection—not requiring hospitalisation	2 (<0·1%)	1 (<0·1%)

(Table 4 continues in next column)

(Continued from previous column)

Data are n (%).

Table 4: **Adverse events**

No anaphylaxis or other serious adverse events were reported in the immediate post-vaccination period, and adverse events were similar between study groups during this period. No serious adverse events related to study vaccine, and no vaccine-related adverse reactions leading to participant discontinuation of the trial, were reported (table 4).

Discussion

The influenza vaccine did not significantly reduce the first co-primary composite outcome (ie, cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke) or the second co-primary composite outcome (ie, recurrent event analysis of cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, or hospitalisation for heart failure) during the entire period of the trial. The vaccine reduced all-cause hospitalisation by 16% and community-acquired pneumonia by 42%. The reduction in all-cause hospitalisation was largely due to the effect of the vaccine reducing heart failure hospitalisations and pneumonia. When events during peak influenza circulation periods were analysed, as prespecified, the first co-primary composite outcome was reduced in participants assigned to influenza vaccine.

During the peak influenza circulation period, secondary outcomes of all-cause death and cardiovascular death were also significantly reduced in the vaccine group compared with the placebo group, as was pneumonia. A similar pattern of fewer events was seen in the seasons when the strain in the vaccine was similar to that of the predominant circulating strain. This generally consistent pattern of lower rates of death and cardiovascular events in the vaccine group than in the placebo group, especially during the peak influenza circulation periods (and even more so in seasons when there was a match between the circulating strain and the vaccine), suggests an important benefit from the use of the influenza vaccine in heart failure patients.

We believe that the co-primary outcomes were not significantly reduced in the vaccine group compared

with in the placebo group because the outcomes included events that were measured during non-peak periods of influenza. That is, vaccination against influenza had only a small effect during periods of low circulation of influenza. The non-fatal myocardial infarction event rates were very low, and so a small effect would not have made a difference to the overall composite outcome.

Our findings of reduced all-cause and cardiovascular deaths in the influenza vaccine group during peak periods of influenza circulation are in keeping with a systematic review and meta-analysis of observational studies of influenza vaccine in patients with heart failure.[26] The review included two studies from Spain and one from the USA, which reported reductions in mortality of between 26% and 41% in vaccinated patients compared with the control groups.[26] Influenza vaccination was associated with a reduction in cardiovascular hospitalisation but not in all-cause hospitalisation.[26] Death rates in our study were higher during periods of peak influenza circulation compared with non-peak periods. The reduction in pneumonia during both peak and non-peak periods of influenza circulation suggested that the benefit might persist beyond the peak circulation period. This ongoing reduction might be related to a lag effect caused by the delay of a bacterial super-infection after influenza infection, although we cannot exclude the possibility that this difference might have arisen by chance. A lag effect might also explain the effect on heart failure hospitalisation during non-peak influenza periods. The marked differences in pneumonia in the overall study, observed during both the peak and off-peak seasons but greater during peak periods, suggest clinically important benefits from influenza vaccination in patients with heart failure.

Although observational studies[27,28] have reported lowered rates of pneumonia associated with the use of the influenza vaccine, randomised controlled trials[29] of influenza vaccine versus controls have been inconclusive because they recorded too few events. To our knowledge, the current study is the largest randomised trial of influenza vaccine versus control (placebo or no vaccine) to assess the effect on pneumonia. The effects in our trial were highly significant clinically or statistically and ranged from a 40% risk reduction in the intention-to-treat analysis to a 50% risk reduction when events during peak influenza circulation were considered. This finding is important, both clinically and in terms of public health.

Our co-primary outcomes differ from those of the Influenza Vaccine After Myocardial Trial (IAMI) study in patients who had previous myocardial infarction, in which participants randomly assigned influenza vaccine had a significantly reduced incidence of all-cause death, myocardial infarction, or stent thrombosis at 12 months compared with those assigned to placebo, during peak seasons.[13] However, when we considered only events during peak influenza circulation periods, our findings were similar to those of the IAMI trial, in that both all-cause and cardiovascular deaths were reduced in the influenza vaccine group.

The strengths of our trial include the inclusion of a large number of individuals at high risk of the outcomes who were followed up over three seasons, high rates of adherence to the protocol, and high rates of follow-up. Study limitations include a reduced duration of intervention and follow-up (a median 2·4 years instead of the planned 3 years) owing to the COVID-19 pandemic and inadequate availability of the vaccine for some countries, with premature termination of their participation in the study. However, our enrolment extended beyond our sample size of 5000. Another limitation is that no adjustments were made for multiple testing of the secondary outcomes, as such adjustments were not prespecified in our analysis plan. Although peak periods of influenza circulation were not always clearly defined in the countries in which this trial took place, we used multiple external sources to estimate these periods. Although our trial was stratified by study site, we acknowledge that without further adjustment for centre, the standard error might have been overly conservative.

Of note, this study was done in regions (including India and China, the two largest countries in the world) in which the use of influenza vaccination is low and there are no reports of benefit. In addition, our results are consistent with results of observational studies. Although this trial was not done in high-income countries, our findings might be generalisable to patients with heart failure, if events occurring during active influenza circulation periods are considered.

Although the prespecified primary outcomes during the entire period of observation were not statistically significant, the reduction during the peak influenza circulating period suggests that there is likely to be a clinical benefit, given the clear reduction in pneumonia, a moderate reduction in hospitalisations, and a reduction in cardiovascular events and deaths during periods of peak circulation of influenza. Taken in conjunction with previous trials and the observational studies, the collective data suggest benefit.

Contributors

ML, HD, AnD and SY conceived the study. PR-M and SIB curated the data and SIB analysed the data. ML, HD, AnD, LMP-V, and SY were responsible for funding acquisition. All authors did the study investigation. ML, HD, PR-M, SIB, and SY were responsible for the methods. ML, VT, AG, TM, and SY did the project administration and supervision. ML wrote the original draft and all authors wrote, reviewed, and edited the manuscript. PR-M and SIB accessed and verified the data.

Declaration of interests

ML reports grants from the Joint Global Health Trials Scheme of the UK Dept for International Development, UK Medical Research Council (MRC), UK National Institute for Health Research, and the Wellcome Trust) and the Canadian Institutes of Health Research (CIHR); in-kind support from Sanofi Pasteur during the conduct of the study; paid participation on advisory boards for Sanofi Pasteur, Medicago,

GlaxoSmithKline, Pfizer, Merck, and Seqirus and on the data safety monitoring board for CanSino Biologics. LMP-V reports grant support from the Wellcome Trust. JZ and YL report grant payments from the Population Health Research Institute to their institution, payment from Bayer, Boehringer Ingelheim, and Novartis for presentations, and travel support from Bayer to attend the European Society of Cardiology 2019 Congress. TM reports grants from CIHR and the Joint Global Health Scheme paid to McMaster University and Hamilton Health Sciences for the conduct of the study. AR, HD, AnD, KK, FG, AlD, KFA, GY, CM, WA, AAM, VT, PR-M, AG, SIB, and SY declare no competing interests.

Data sharing

We will comply with the principles of the MRC policy on data sharing of intervention studies. Controlled access to data will be given to other research groups provided that there is evidence of ethics approval to support the request for access and that the process will be collaborative with the the principal and other investigators. Such requests will be reviewed internally. Data-sharing agreements will include the criteria identified in the MRC Policy and Guidance on Sharing Research Data from Population and Patient Studies. Individual de-identified participant data (including data dictionaries) will be shared; no other related documents (eg, study protocol, statistical analysis plan, etc) will be available. The data will become available in July 2023, for 6 months. Requests by other research groups for access to data for meta-analysis can be made by contacting the correspondence author.

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